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□ Case Report □

Dermatomyositis Associated with Gallbladder Cancer

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Dermatomyositis, an idiopathic inflammatory myopathy with characteristic skin manifestations, is associated with several types of cancer. Only three cases of gallbladder cancer with dermatomyositis have been reported worldwide, and none has been reported in Korea. We present a case of a 71-year-old male with proven dermatomyositis associated with gallbladder cancer to emphasize the necessity of work-up for malignancies with low incidence in patients with inflammatory myopathies.

Key Words. **Dermatomyositis, Gallbladder cancer, Malignancy, Inflammatory myopathy**

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal muscle weakness and typical skin lesions such as a heliotrope rash and Gottron's papules (1).

An association between malignancy and inflammatory myopathy was first suspected as early as 1916 when the simultaneous occurrence of polymyositis and gastric carcinoma was reported by Stertz (2). Since then, much effort has been made to clarify the mechanism of inflammatory myopathy accompanied by malignancy (3). Nevertheless, this has not been accomplished.

A wide range of prevalence from 4% to 42% of malignancy in patients with DM has been reported (4). Among cancers associated with inflammatory myopathies, adenocarcinomas of cervix, lung, ovaries, pancreas, bladder, and stomach account for the majority of cases (5). However, common types of malignancies occurring with inflammatory myopathies do not follow the rank-order pattern of cancer incidence for a given region and race (6)

To our knowledge, only three cases of DM accompanied by gallbladder (GB) cancer have been reported worldwide to date, and none has been reported in Korea. Therefore, we describe the first patient with DM accompanied by GB cancer at the diagnosis of DM in Korea.

Case Report

A 71-year-old male patient was admitted for an itchy facial rash and pain in the proximal muscles of the upper and lower extremities and around the neck, which had gradually worsened for 6 months. The patient had no medical history except for hypertension.

On admission, he was conscious and alert, and his vital signs were within normal ranges. He exhibited DM-associated skin rashes: a heliotrope rash on both eyelids, Gottron's papules on the right hand, V sign, Shawl sign, and itchy rashes on his forehead, left anterior chest wall, bilateral shoulders, and elbow joints (Figure 1).

Neurologic examination showed that his motor strength in the proximal portions of bilateral upper and lower extremities was reduced from grade 3/5 to 4/5 without sensory dysfunction. Muscle weakness of grade 4/5 was also observed during neck flexion. A squatting test could not be performed due to myalgia and muscle weakness.

Laboratory tests showed a white blood cell count of 3,700 /μL, hemoglobin concentration of 11.0 g/dL, platelet count of 133,000/μL, erythrocyte sedimentation rate of 44 mm/hr,

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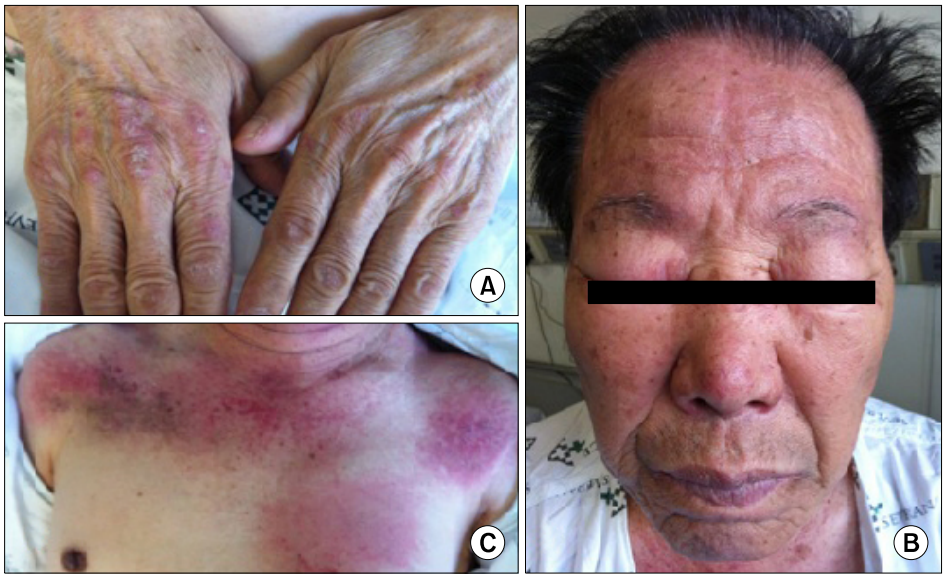

Figure 1. (A) Gottron's papules on the right hand. (B) Heliotrope rash and a forehead erythematous patch. (C) V sign, Shawl sign, and erythematous patches on both shoulders and the left anterior chest wall.

and C-reactive protein concentration of 8.26 mg/L. The levels of aspartate transaminase, alanine transaminase, and lactate dehydrogenase were 56, 28, and 381 IU/L, respectively. Creatine phosphokinase and aldolase concentrations were elevated to 479 IU/L (normal range: 35～200 IU/L) and 11.1 u/mL (normal range: 0～8 u/mL), respectively. Viral serologic tests for hepatitis B and C were negative. Rheumatoid factor (42.4 IU/mL) and anti-nuclear antibody (1 : 40, speckled pattern) were positive. The titer of anti-double-stranded DNA antibody was slightly elevated to 112.8 AU (normal range: ＜92.6 AU). Other autoantibodies including anti-Jo1, anti-ribonucleoprotein, and anti-Scl were not detected.

Skin punch biopsies of rashes on his eyelids and forehead revealed epidermal atrophy with basal keratinocyte vacuolar degeneration and cytoid bodies in the dermo-epidermal junction.

Electromyography and nerve conduction velocity tests suggesting myositis were as follows: [1] mild to moderate numbers of fibrillation potentials mixed with positive sharp waves, [2] brief and small amplitudes, and [3] polyphasic motor unit action potentials with full interference patterns in the right biceps brachii muscle. Normal electromyography results were obtained for the right fist dorsal interossei, tibialis anterior, and vastus medialis muscles.

Collectively, we diagnosed the patient with DM and performed a malignancy work-up protocol, including positron emission tomography/computed tomography (PET/CT), esophagogastroduodenoscopy, colonoscopy, and serum tumor marker testing, which was suggested to perform in our previous report (6). The patient had increased serum levels of carcinoembryonic antigen (57.77 ng/mL) and carbohydrate antigen

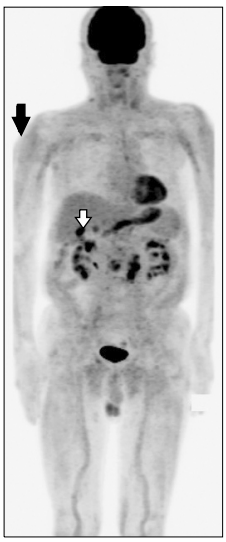

Figure 2. PET/CT scan. Diffuse and mild fluorodeoxyglucose uptake in skeletal muscle was seen (black arrow), which likely indicates inflammatory changes due to dermatomyositis involvement. Fluorodeoxyglucose uptake in the disrupted gallbladder wall (white arrow) and pericholecystic fat infiltration in the gallbladder body were seen.

19～9 (645.0 U/mL), but other tumor markers, including prostate-specific antigen and squamous cell carcinoma antigen, were normal. PET/CT showed GB cancer with regional and para-aortic lymph node metastasis, as well as diffuse and mild fluorodeoxyglucose uptake in the skeletal muscles (Figure 2).

Studies for the staging work-up, including biliary dynamic CT (Figure 3), pancreatobiliary MRI, and endoscopic ultrasonography, were performed and they revealed the stage to be T3N2M0 (T3: pericholecystic fat infiltration, N2: para-aortic lymph node enlargement), which is inoperable. Instead, de-

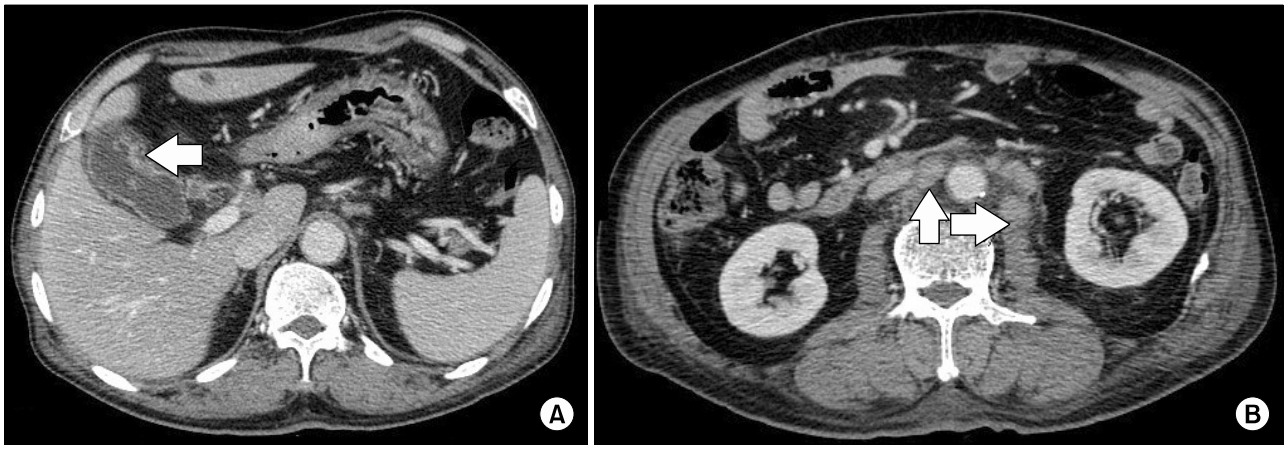

Figure 3. Biliary dynamic CT scan. (A) Irregular wall thickening of the gallbladder with pericholecystic fat infiltration and GB cancer with serosa invasion (T3). (B) Enlarged lymph nodes were seen at the cystic duct, portahepatis, portocaval, and bilateral para-aortic space, which are suggestive of metastatic lymph nodes.

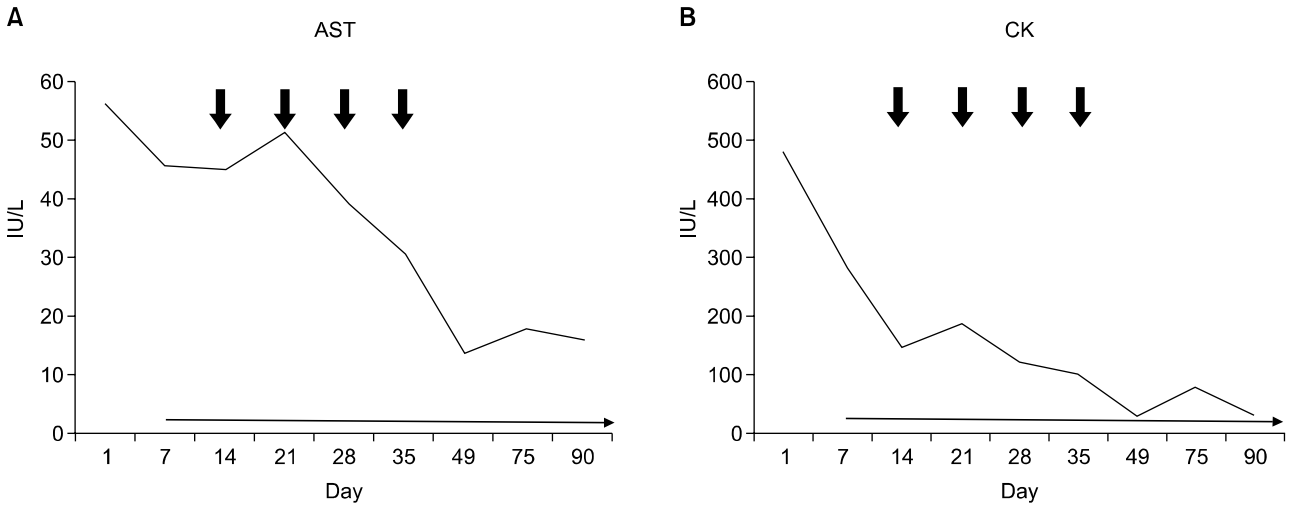

Figure 4. Changes in muscle enzyme levels. (A) aspartate aminotransferase (AST, normal range: 13.0～34.0 IU/L), (B) creatine phosphokinase (CK, normal range: 44～245 IU/L); day 1: admission, day 7: beginning administration of low-dose prednisolone, day 14-day 49: concurrent chemoradiotherapy, day 75: CT imaging after concurrent chemoradiotherapy, day 90: planned chemotherapy, long arrow: administration of prednisolone, short arrows: 5-FU administration.

finitive concurrent chemoradiotherapy based on weekly 5-fluorouracil (500 mg/m^2 each time, total of five times) was started for GB cancer.

We did not use a high dose of glucocorticoids or immunosuppressive agents since we expected that the immunosuppressive effect of the chemotherapy would improve DM. For the skin lesions, we administered 8 mg/day methylprednisolone, 15 mg/day meloxicam, and 20 mg/day hydroxyzine.

After 6 weeks, partial response of GB cancer was observed. Most of the skin lesions disappeared with little hyperpigmentation. The patient continued treatment with methylprednisolone (8 mg) alone for DM. The patient's muscle power of both the proximal upper and lower extremities improved from grade IV to grade V, and the patient became able to walk without assistance. All the muscle enzymes decreased to normal range, with levels of aspartate transaminase, alanine transaminase, lactate dehydrogenase, creatine phosphokinase, and aldolase of 19 IU/L, 16 IU/L, 184 IU/L, 18 IU/L, and 6.0 u/mL, respectively (Figure 4). Further chemotherapy was planned for GB cancer. However, chemotherapy was infeasible since bleeding from peptic ulcer and non-ST elevation myocardial infarction were occurred. He died of acute renal failure resulting from peritoneal carcinomatosis as GB cancer progressed.

Discussion

According to the Korean Central Cancer Registry in 2009, the age-adjusted incidence rate of cancer was 282 per 100,000 people per year. The leading cancer sites were thyroid, stomach, colon, lung, liver, breast, and prostate. The incidence of GB and other/unspecified parts of the biliary tract accounted for only 2.4% (7).

Several risk factors have been identified for GB cancer, many of which share a common characteristic of chronic GB inflammation: old age, female sex, benign GB disease (mainly gallstones and polyps), family history of GB disease, body mass index higher than 30, high parity and number of pregnancies, oral contraceptive use, and carrier state of *Salmonella typhi, Salmonella paratyphi, Helicobacter bilis,* and *Helicobacter pylori* in bile specimens (8). In addition, congenital biliary cyst, abnormal pancreatobiliary duct junction, and smoking are also known risk factors for GB cancer (8). However, the patient in this case report had no such risk factors for GB cancer except old age.

A population-based retrospective cohort study of 537 patients with idiopathic inflammatory myopathy in Australia reported that 104 patients (116 cases) developed malignancies (4). A temporal relationship was found in 36% of the 104 patients who were diagnosed with malignancies within approximately 7 days of confirmation of myopathy. According to a study conducted in Japan by Kohei, among 136 patients with inflammatory myopathy, the frequency of malignancy associated with DM was 24% (9). Malignancies of stomach, colon, ovary, lung, thymus, pancreas, breast, and lymph node were found. A study of 41 Korean patients showed that the prevalence of malignancy in Korean patients with DM was 31.3% (6). Malignancies of breast, gastrointestinal tract, thyroid, thymus, lung, nasopharynx, pleura, and bladder were observed. An extensive literature review revealed that this case report is the first case of GB cancer associated with inflammatory myopathy to be reported in Korea.

As mentioned above, only three cases of DM accompanied by GB cancer have been reported worldwide to date (Table 1) (10-12). All the three patients were treated with high-dose glucocorticoids for DM. GB cancer was detected by cancer screening tests after diagnosis of DM in two cases and was found with an autopsy in the last case. Only one case had risk factors for GB cancer such as obesity and multiple gallstones. In two out of three cases, patients with dysphagia at the time of diagnosis died of aspiration pneumonia. The treatment for GB cancer in these three cases was not reported for two patients died and one patient, whose cancer was operable, did not follow up. Therefore, our case has clinical significance in that this is the first case where both GB cancer and DM improved with chemoradiotherapy targeting GB cancer.

The mechanism of the association between inflammatory myopathy and cancer is uncertain; however, several hypotheses have been proposed. Casciola-Rosen et al. reported that muscle-specific autoantigens, such as Mi-2, HRS, and DNA-PKcs are frequently expressed at low levels in a variety of normal muscle tissues, but at increased levels in regenerating cells in myositis muscle (13). Furthermore, the same antigens are also expressed at high levels in breast cancer, lung adenocarcinoma, and hepatocellular carcinoma, but not in corresponding normal tissue (13). Since these antigens are expressed in both myositis and cancer tissue, we assumed that these antigens may cross-react with cancer tissue, and this may contribute to development of DM with malignancy.

Table 1. Comparison of three cases of dermatomyositis accompanied by gallbladder cancer that have been reported to date plus this case

	Age (yrs)/ Sex	Autoantibody	Symptoms	DM treatment	GB cancer risk factors	Cancer status & treatment	Outcome
2002. Greece	75/F	ANA 1 : 160 positive	Weakness Dysphagia Dyspepsia	High-dose steroids	Obesity Multiple gallstones	Inoperable at explo-laparotomy finding, observation	Expired due to pneumonia
2005. India	44/M	ANA, anti-Jo1 negative	Weakness	High-dose steroids	NM	Operable, consider operation	Lost at follow-up
2011. India	65/F	ANA 1 : 40 positive, anti-Jo1, anti-Scl, anti-RNP negative	Weakness Dysphagia	High-dose steroids	NM	Diagnosis at autopsy	Expired due to pneumonia
2012. Korea	71/M	ANA 1:40 positive, anti-Jo1, anti-Scl, anti-RNP negative	Weakness	Low-dose steroids	Old age	Inoperable at imaging study, CCRT	Expired ue to cancer progression

F: female, M: male, ANA: anti-nuclear antibody, NM: not mentioned.

The general treatment for DM is administration of corticosteroids until clinical improvement of skin lesions and muscle weakness is achieved, and the dosage is gradually tapered off. Immunosuppressive agents such as methotrexate, azathioprine, and cyclosporine, biological agents, and intravenous immunoglobulin have proven beneficial for patients who are refractory to corticosteroids (14). However, some reports have described an improvement in DM without immunosuppressive drugs after chemotherapy or even after surgery (15,16). In addition, the clinical symptoms of our patient markedly improved with low-dose glucocorticoids alone after the initiation of cancer treatment. We believe that these results were due to the immunosuppressive effects of systemic chemotherapy.

Summary

DM is well known to be associated with various types of cancer. However, DM with GB cancer is a rare condition, and only three cases have been reported in the literature worldwide, with none in Korea. We report a rare case of DM accompanied by GB cancer in a patient who had no risk factors for GB cancer and who improved during cancer treatment. We expect our case report to emphasize the importance of a malignancy work-up, including for cancers with low incidence, in patients with inflammatory myopathy.

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